CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74769

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 74-769 Date of Submission: December 31, 1996

Applicant's Name: AB Generics L.P.

Established Name: Morphine Sulfate Extended-Release Tablets, 100 mg and 200 mg

Labeling Deficiencies:

1. CONTAINER (100s)

   We encourage the use of boxing, contrasting colors, or other means to differentiate the strengths of your products.

2. INSERT (100 mg and 200 mg)

   a. GENERAL

      You may revise "Morphine Sulfate" to read "morphine sulfate" throughout the text of the insert, (note lower case).

   b. TITLE

      ...Tablets... (Plural)

   c. DESCRIPTION

      i. Include the molecular weight; 758.85.

      ii. Include the molecular formula; $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$

   d. CLINICAL PHARMACOLOGY

      i. Revise the subsection heading, "Pharmacodynamics" so that it has the same prominence as the subsection heading, "Metabolism and Pharmacokinetics".

      ii. Pharmacodynamics (Plasma Level-Analgesia Relationships)

      Revise "ml" in the last line to read "mL".

e. PRECAUTIONS

i. Pregnancy (Teratogenic Effects - CATEGORY C)

Replace the first paragraph with the following text:

Adequate animal studies on reproduction have not been performed to determine whether morphine affects fertility in males or females. There are no well-controlled studies in women, but marketing experience does not include any evidence of adverse effects on the fetus following routine (short-term) clinical use of morphine sulfate products. Although there is clearly defined risk, such experience cannot exclude the possibility of infrequent or subtle damage to the human fetus.

Morphine sulfate extended-release tablets should be used in pregnant women only when clearly needed. (See also: PRECAUTIONS: Labor and Delivery, and DRUG ABUSE AND DEPENDENCE.).

ii. Pediatric Use

Revise this subsection to read as follows:

Use of morphine sulfate extended-release tablets has not been evaluated systematically in pediatric patients.

f. DOSAGE AND ADMINISTRATION

i. Conversion from Conventional Oral Morphine to Morphine Sulfate Extended-Release Tablets

Add the following text as the last 3 sentences in this subsection:

Morphine sulfate extended-release tablets of 15 mg strength should be used for initial conversion for patients whose total daily requirement is expected to be less than 60 mg. Morphine sulfate extended-release tablets of 30 mg strength are recommended for patients with a daily morphine requirement of 60 to 120 mg. When the total daily dose is expected to be greater than 120 mg, the appropriate combination of tablet strengths should be employed.

ii. Conversion from Parenteral Morphine or Other Opioids (Parenteral or Oral) to Morphine Sulfate Extended-Release Tablets

Add the following text as the last 2 sentences in the first paragraph:

In patients whose daily morphine requirements are expected to be less than or equal to 120 mg per day, morphine sulfate extended-release tablets of 30 mg strength are recommended for the initial titration period. Once a stable dose regimen is reached, the patient can be converted to the 60 mg or 100 mg morphine sulfate extended-release tablets, or an appropriate combination of tablet strengths, if desired.

iii. Use of Morphine Sulfate Extended-release Tablets as the first opioid analgesic (See also comment [vii. B)] below)

Replace the first two sentences with the following text:

There has been no systemic evaluation of morphine sulfate extended-release tablets as an initial opioid analgesic in the management of pain.

iv. Considerations in the Adjustment of Dosing Regimens

Add the following text as the third paragraph:

For patients with low daily morphine requirements, morphine sulfate extended-release tablets of 15 mg strength should be used.

v. Conversion from Morphine Sulfate Extended-release Tablets to Parenteral Opioids (Insert for 100 mg strength)

Revise the subsection heading as above and make the following revision in the first sentence (delete reference to 100 mg strength):

...patient from morphine sulfate...

vi. The following comments are specific to the insert submitted for the 200 mg strength and

are in addition to the above comments:

A) Conversion from Parenteral Morphine or Other Opioids (Parenteral or Oral) to Morphine Sulfate Extended-Release Tablets

1) Revise the subsection heading as above (plural "Tablets") and make the following revision in the penultimate sentence of the second paragraph, "...converting a patient to morphine sulfate extended-release tablets directly. The...".

2) 2. Other parenteral...

Make the following revision in the second paragraph, "...daily dose of morphine sulfate extended-release tablets required and rely...".

B) Add the subsection, "Use of Morphine Sulfate Extended-release Tablets as the first Opioid Analgesic" with the revisions outlined above.

C) Special Instructions for Morphine Sulfate Extended-release Tablets 200 mg

Make the following revision in the last sentence, "...**regimen using lower strengths of extended-release morphine sulfate tablets or other opioids.**".

Please revise your container labels and package insert labeling, as instructed above, and submit final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research